REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following remarks.

I. Status of the Claims

Claims 4, 44, 47, 61 and 90 are amended to correct typographical errors. Claims 13, 55 and 70 are currently amended to delete trademarks. Finally, Claim 58 is amended to recite a method of treating diabetes in a subject in need thereof. Support for the amendment to claim 58 can be found, *inter alia*, at page 3 of the published patent application, paragraph [0021], and page 13, paragraph [0177].

As the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested. Upon entry of the foregoing amendments, claims 1-90 will be pending in the application, with 1, 40 and 58 being the independent claims.

II. The Objection to the Claims

The Office Action, at page 2, objects to claim 44 for allegedly containing a typographical error. As the foregoing amendment corrects the typographical error, the objection is moot and its withdrawal is respectfully requested.

III. The Rejections Under 35 U.S.C. § 112, First Paragraph

A. Written Description

The Office Action, at pages 2-3, rejects claims 25-35 and 76-86 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. Specifically, the Office Action states that the claims do not identify the structure, material or acts that would be capable of carrying out the functional properties recited in the claims. Applicants respectfully traverse this ground for rejection.

Claim 1 reads:

> A composition comprising: (a) particles of glipizide or a salt thereof, ***wherein the glipizide particles have an effective average particle size of less than about 2000 nm***; and (b) at least one surface stabilizer.

Claim 58 reads:

> A method of treating diabetes in a subject in need thereof comprising administering to the subject an effective amount of a composition comprising: (a) particles of a glipizide or a salt thereof, ***wherein the glipizide particles have an effective average particle size of less than about 2000 nm***; and (b) at least one surface stabilizer.

The main feature of the glipizide particles recited in the claims of the present application is that they have ***an effective average particle size of less than about 2000 nm.*** This effective average particle size provides the compositions of the invention with a specific pharmacokinetic profile that includes: (1) a T_{max} for the glipizide, when assayed in the plasma following administration, that is less than the T_{max} for a non-nanoparticulate glipizide formulation administered at the same dosage; (2) a C_{max} for the glipizide, when assayed in the plasma following administration, that is greater than the C_{max} for a non-nanoparticulate glipizide formulation administered at the same dosage; and (3) an AUC for glipizide, when assayed in the plasma of a mammalian subject following administration, that is greater than the AUC for a non-nanoparticulate glipizide formulation administered at the same dosage. *See* published application at page 5, paragraph [0051].

The effective average particle size of less than 2000 nm is the feature required to provide the glipizide particles of the invention the unique functional properties listed above. Indeed, the published application at page 6, paragraphs [0066] and [0067], states the following:

> *An additional feature of the nanoparticulate glipizide compositions of the invention is that the compositions*

> *redisperse such that the effective average particle size of the redispersed glipizide particles is less than about 2 microns. This is significant, as if upon administration the nanoparticulate glipizide particles present in the compositions of the invention did not redisperse to a substantially nanoparticulate particle size, then the dosage form may lose the benefits afforded by formulating glipizide into a nanoparticulate particle size.*
>
> *This is because nanoparticulate glipizide compositions benefit from the small particle size of glipizide; if the nanoparticulate glipizide particles do not redisperse into the small particle sizes upon administration, then "clumps" or agglomerated glipizide particles are formed. With the formation of such agglomerated particles, the bioavailability of the dosage form may fall.*

[Emphasis added].

Accordingly, the structure that provides the features claimed in claims 25-35 and 76-86 is clearly and positively specified. As such, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

B. Enablement

The Office Action, at page 3, rejects claims 25-35 and 76-86 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. Specifically, the Office Action states that the claims lack the description of the possible genus with the recited functional characteristics. Applicants respectfully traverse this ground for rejection.

As stated above, the main feature of the glipizide particles of the invention is that they have an effective average particle size of less than about 2000 nm. This effective average particle size provides the glipizide compositions of the present application with the specific pharmacokinetic functional characteristics - T_{max}, C_{max} and AUC –recited in certain dependent claims.

Furthermore, the specification provides extensive disclosure of the glipizide particles, their properties and pharmacokinetic and re-dispersibility profiles, and methods of making and using nanoparticulate formulations comprising the glipizide particles. *See* pages 5-14 of

the published application. Examples 1-4 in the disclosure describe the preparation of nanoparticulate glipizide compositions.

Clearly, the specification provides extensive disclosure to enable one skilled in the art to make and/or use the claimed invention. Thus, the claimed invention is fully enabled. As such, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

IV. The Rejections Under 35 U.S.C. § 112, Second Paragraph

The Office Action, at pages 3-4, rejects claims 13, 55 and 58-90 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. Specifically, claims 13, 55 and 70 are rejected for containing trademarks, and claim 58 is rejected because the method of treatment is unclear. Applicants respectfully traverse this ground of rejection.

Solely to advance prosecution and not in acquiescence with the rejection, the foregoing amends claims 13, 55 and 70 to delete trademarks and claim 58 to recite a method of treating diabetes in a subject in need thereof. Accordingly, the rejection under 35 U.S.C. § 112, second paragraph, is moot and its withdrawal is respectfully requested.

V. The Provisional Nonstatutory Obviousness-Type Double Patenting Rejections

A. The Provisional Rejections Over Copending U.S. Patent Applications Nos. 10/619,539 and 09/337,675

The Office Action, at pages 4-5, provisionally rejects claims 1-15 and 17-57 on the ground of nonstatutory obviousness-type double patenting, as being allegedly unpatentable over claims 1-75 of co-pending U.S. Patent Application No. 10/619,539. Further, the Office Action provisionally rejects claims 1-15 and 17-57 on the ground of nonstatutory obviousness-type double patenting, as being allegedly unpatentable over claims 1-54 of co-pending U.S. Patent Application No. 09/337,675. Applicants respectfully traverse these grounds of rejections.

Co-pending U.S. Patent Applications Nos. 10/619,539 and 09/337,675 have not yet been allowed, thus, the rejections remain only provisional rejections. Applicants respectfully request that these rejections be held in abeyance until allowable subject matter is found in either this application or in co-pending U.S. Patent Applications Nos. 10/619,539 and 09/337,675.

B. The Provisional Rejection Over Co-Pending Application No. 10/697,703 In View Of U.S. Patent No. 6,383,471

The Office Action, at page 6, provisionally rejects claims 1-15 and 17-57 on the ground of nonstatutory obviousness-type double patenting, as being allegedly unpatentable over claims 1-62 of co-pending U.S. Patent Application No. 10/697,703 (the "'703 application") in view of U.S. Patent No. 6,383,471 (the "'471 patent"). Applicants respectfully traverse this ground of rejection.

1. Summary of the Claimed Invention

The presently claimed invention is directed to a composition comprising particles of glipizide or a salt thereof having an effective average particle size of less than about 2000 nm, and at least one surface stabilizer. Further, the invention is directed to a method of producing a glipizide composition, where the resultant particles have an effective average particle size of less than about 2000 nm.

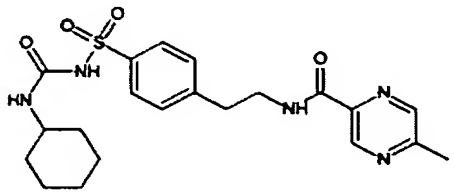
2. The Cited References Fail To Teach Each And Every Element of the Claimed Invention

The claims of co-pending U.S. Patent Application No. 10,697,703 are directed to a *nimesulide* composition comprising particles of nimesulide or a salt thereof having an effective average particle size of less than about 2000 nm; and at least one surface stabilizer. The claims are also directed to a method of producing the nimesulide composition of the invention.

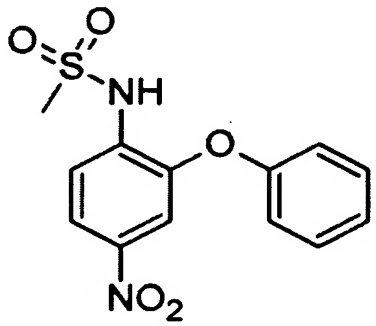
The Office Action recognizes that the '703 application does not claim, disclose or suggest *glipizide* compositions. Nevertheless, the Office Action relies on the disclosure of the '471 patent for the teachings that hydrophobic therapeutic agents having at least one

ionizable functional group include glipizide and nimesulide, and infers from those teachings that glipizide and nimesulide are equivalent.

The '471 patent, however, does not stand for such a conclusion. Glipizide is a second generation sulfonyl urea used to treat noninsulin-dependent (Type II) diabetes mellitus (NIDDM). Glipizide lowers blood sugar by stimulating the pancreas to secrete insulin and helping the human body to use insulin more efficiently. Glipizide has the following structure:



Nimesulide, on the other hand, is a sulphonanilide non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties, used for the symptomatic treatment of inflammation and pain. Nimesulide has the following structure:



It is clear that glipizide and nimesulide are not equivalent, as they differ in structure and functional properties.

For at least these reasons, the provisional nonstatutory obviousness-type double patenting rejection of claims 1-15 and 17-57 is improper. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

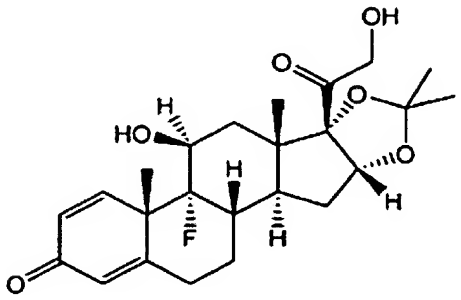
C. The Provisional Rejection Over Co-Pending Application No. 10/697,716 In View Of U.S. Patent No. 5,654,005

The Office Action, at pages 6-7, provisionally rejects claims 1-15 and 17-57 on the ground of nonstatutory obviousness-type double patenting, as being allegedly unpatentable over claims 1-65 of co-pending U.S. Patent Application No. 10/697,716 (the "'716 application") in view of U.S. Patent No. 5,654,005 (the "'005 patent"). Applicants respectfully traverse this ground of rejection.

The claims of co-pending U.S. Patent Application No. 10,697,716 are directed to a *triamcinolone* composition comprising particles of triamcinolone or a salt thereof having an effective average particle size of less than about 2000 nm; and at least one surface stabilizer. The claims are also directed to a method of producing the triamcinolone composition of the invention.

The Office Action recognizes that the '716 application does not claim, disclose or suggest *glipizide* compositions. Nevertheless, the Office Action relies on the disclosure of the '005 patent for the teachings that water-insoluble medicaments that can be used in a controlled release dosage form include glipizide and nimesulide, and deduces from those teachings that glipizide and triamcinolone are equivalent.

Triamcinolone, however, is a steroid used in the treatment of endocrine, immune and allergic disorders, and has a structure, which is different from the structure of glipizide, as shown below:



It is clear that glipizide and triamcinolone are not equivalent, as they differ in structure and functional properties.

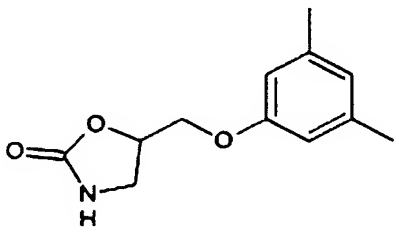
For at least these reasons, the provisional nonstatutory obviousness-type double patenting rejection of claims 1-15 and 17-57 is improper. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

D. The Provisional Rejection Over Co-Pending Application No. 10/912,552

The Office Action, at page 7, provisionally rejects claims 1-15 and 17-57 on the ground of nonstatutory obviousness-type double patenting, as being allegedly unpatentable over claims 1-36 of co-pending U.S. Patent Application No. 10/912,552 (the "'552 application"). Applicants respectfully traverse this ground of rejection.

The claims of co-pending U.S. Patent Application No. 10,912,552 are directed to a *metaxalone* composition comprising particles of metaxalone or a salt thereof having an effective average particle size of less than about 2000 nm; and at least one surface stabilizer. The claims are also directed to a method of producing the metaxalone composition of the invention. Claim 17 in the '552 application is drawn to a metaxalone composition additionally comprising one or more non-metaxalone active agents, and includes glipizide in the laundry list of active agents that may be included in the metaxalone composition.

Metaxalone is a muscle relaxant used for short-term painful muscular conditions, and has the following structure:



Clearly, glipizide and metaxalone differ in structure and functional properties.

The specification of the '552 application, at paragraph [0110], teaches that non-metaxalone active agents can be present in the metaxalone compositions of the invention in a crystalline, amorphous, semi-crystalline, semi-amorphous phase, or a mixture thereof.

Further, at paragraph [0111], the specification teaches that the non-metaxalone compound can be formulated separately from, or co-formulated with the nanoparticulate metaxalone composition, and specifically states that *"[w]here a nanoparticulate metaxalone composition is co-formulated with a second active agent, the second active agent can be formulated in any suitable manner, such as immediate-release, rapid-onset, sustained-release, or dual-release form."*

The '552 application does not claim, disclose or suggest **two** elements of the claimed invention. First, the '552 application does not disclose or suggest a composition comprising particles of glipizide or a salt thereof. Instead, the '552 application provides the general teaching that any additional active agent, including glipizide, may be formulated for immediate or sustained release in the metaxalone compositions. Second, the '552 application does not disclose or suggest particles of glipizide having an effective average particle size of less than about 2000 nm.

The Office Action alleges that it would have been obvious to one skilled in the art to prepare the claimed invention, because the '552 application teaches the use of the claimed active ingredient in the same dosage form for the same release rate. This allegation, however, is impermissible, in view of the teachings of the specification of the '552 application reported above. The teaching or suggestion to make the claimed invention must be found in the cited reference, and not based on Applicants' disclosure.

Thus, for the reasons stated above, the rejection is improper. Reconsideration and withdrawal of this rejection is therefore respectfully requested.

VI. The Rejections Under 35 U.S.C. § 103

1. The Rejection Over Liversidge in view of Kuczynski

The Office Action, at pages 7-9, rejects claims 1-8, 10-11, 13-15, 17-35, 40-43, 45-50, 52-53, 55-65, 67-68 and 70-90 under 35 U.S.C. § 103(a) as being allegedly unpatentable over U.S. Patent No. 5,145,684 to Liversidge *et al.* ("Liversidge") in view of U.S. Patent No.

5,024,843 to Kuczynski *et al.* ("Kuczynski"). Applicants respectfully traverse this ground of rejection.

The Patent Office bears the initial burden of factually supporting any *prima facie* conclusion of obviousness under 35 U.S.C. § 103. The MPEP § 2142 sets forth the criteria necessary to satisfy this burden:

> To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.
>
> The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As discussed below, there is no prima facie case of obviousness, because none of these three criteria is satisfied.

A. The Cited References Fail to Teach Each and Every Element of the Claimed Invention

The primary reference, Liversidge, discloses particles consisting essentially of a crystalline drug having a surface modifier adsorbed on the surface in an amount sufficient to maintain an effective average particle size of less than about 400 nm. *See* col. 2, lines 30-42. Liversidge discloses a lengthy list of classes of drugs, including antidiabetic agents, that could be used to form a nanoparticulate active agent composition. *See* col. 3, line 53 to col. 4, line 13. However, Liversidge makes no mention of glipizide, nor are antidiabetic agents even a "preferred" class of drugs. Thus, Liversidge fails to teach or suggest nanoparticulate glipizide compositions. Furthermore, Liversidge fails to disclose or suggest the unexpected pharmacokinetic properties of the glipizide nanoparticle compositions of the present invention.

The Office Action recognizes the deficiencies of Liversidge, and relies on the disclosure of Kuczynski for the teachings that glipizide is an antidiabetic drug. Kuczynski, however, does not remedy the deficiencies of Liversidge. Kuczynski discloses a composition comprising *granules of 2 to 50 mg of glipizide*. Kuczynski, like Liversidge fails to teach or suggest nanoparticulate glipizide compositions.

B. There is no Motivation or Suggestion to Combine the References

The Office Action maintains that Liversidge suggests nanoparticulate compositions comprising antidiabetic agents, and infers from these teachings that one of skill in the art would scour the literature for specific antidiabetic agents, specifically glipizide, and formulate them into nanoparticulate active agent compositions. Thus, according to the Office Action, one of skill in the art would turn to Kuczynski, select glipizide, and use glipizide in the nanoparticulate compositions of Liversidge, for the following reasons:

> Thus, it would have been obvious to one of ordinary skill in the art to select glipizide as an anti-diabetic agent in view of the teachings of Kuczynski , because Kuczynski teaches glipizide is [sic] a known antidiabetic agent in pharmaceutical art, and because Kuczynski teaches glipizide in odorless and advantage [sic] antidiabetic agent useful for the treatment of diabetes.

Office Action at pages 8-9.

In essence, the Office Action reasons that since Liversidge lists antidiabetic agents as a class of drugs from which "[s]uitable drug substances can be selected", one skilled in the art would search the literature and form nanoparticulate compositions of *every* antidiabetic agent, including glipizide.

Such reasoning cannot adequately support the obviousness rejection, because the rationale fails to provide a clear motivation as to why one of skill in the art would select glipizide from among the many known antidiabetic agents. It is not enough for the prior art to disclose glipizide as an antidiabetic agent, because "[s]ome motivation to select the claimed species ... must be taught by the prior art." *See MPEP § 2144.08(II)(A)(4)(a). See also In re Deuel*, 51 F.3d at 1558-59, 34 USPQ2d 1210, 1215 ("No particular one of these DNAs can be

obvious unless there is something in the prior art to lead to the particular DNA and indicate that it should be prepared"). This requirement that the motivation be specific to the recited species stems from the well-established tenet that "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious" *See MPEP § 2143.01(III). See also In re Brouwer*, 77 F.3d 422, 425, 37 USPQ2d 1663, 1666 (Fed. Cir. 1996).

In this case, the prior art lacks such a motivation to select glipizide from among many antidiabetic agents. In fact, the Office Action offers no rationale to specifically select glipizide and relies entirely on the fact that "*glipizide is a known antidiabetic agent in pharmaceutical art.*" As discussed above, it is not enough that one of skill in the art "be able to choose" a specific species. There must be a motivation to select the species, and such motivation to arrive at the presently claimed invention is lacking.

C. One of Skill in the Art Would Have no Expectation of Success

One of skill in the art would not have a reasonable expectation of success in modifying the nanoparticulate compositions of Liversidge to include glipizide, because Liversidge warns against indiscriminate selection of drugs. Specifically, Liversidge teaches that "not every combination of surface modifier and drug substance provides the desired results" *See id* at col. 7, lines 21-23. This is due in part to the requirement that the surface modifier adsorb to the surface of the drug substance. Indeed, Liversidge teaches that "[t]he surface modifier is adsorbed on the surface of the drug substance in an amount sufficient to maintain an effective average particle size of less than about 400 nm." *See id.* at col. 5, lines 13-15. The adsorption of the surface stabilizer to the drug substance is essential in the formation of stable nanoparticles. Thus, one of skill in the art would not have known *a priori* whether or not a surface stabilizer would adsorb to any particular drug, such as glipizide. Accordingly, one of skill in the art would not have a reasonable expectation of success in modifying the references to arrive at the claimed invention.

The absence of a reasonable expectation of success is underscored by Liversidge's Comparative Examples A-F. *See id* at cols. 14-15. These examples confirm that selection of

surface modifiers and drug substances is not a trivial endeavor and that some combinations fail to result in suitable compositions. Such demonstrated failures prevent one of skill in the art from having any reasonable expectation of success and offer, at best, a hope for success. Accordingly, the evidence of record militates against any finding of a reasonable expectation of success.

For at least these reasons, the rejection of claims 1-8, 10-11, 13-15, 17-35, 40-43, 45-50, 52-53, 55-65, 67-68 and 70-90 under 35 U.S.C. § 103(a) is improper. Accordingly, reconsideration and withdrawal of this ground of rejection is respectfully requested.

2. The Rejection Over Liversidge in view of Kuczynski and Parikh

The Office Action, at pages 9-10, rejects claims 9, 12, 44, 51, 54, 66 and 69 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Liversidge in view of Kuczynski and international application WO 98/07414 to Parikh et al. ("Parikh"). Applicants respectfully traverse this ground of rejection.

The inability of Liversidge and Kuczynski to teach or suggest the invention of claims 1-8, 10-11, 13-15, 17-35, 40-43, 45-50, 52-53, 55-65, 67-68 and 70-90 is demonstrated above. The additional reference, Parikh, does not remedy the deficiencies of Liversidge and Kuczynski. Rather, the disclosure of Parikh is directed to compositions comprising microparticles of water-insoluble drugs and methods of producing these compositions. Parikh fails to teach or disclose nanoparticulate glipizide compositions and thus fails to remedy the deficiencies of Liversidge and Kuczynski.

For at least this reason, the rejection is improper. Accordingly, Applicants respectfully request reconsideration and withdrawal of this ground of rejection.

CONCLUSION

Applicants believe that all of the stated grounds of objections and rejections have been properly traversed or rendered moot. The present application is now in condition for allowance. Favorable reconsideration of the application is therefore respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date January 10, 2007

By _____

FOLEY & LARDNER LLP
Customer Number: 31049
Telephone: (202) 672-5538
Facsimile: (202) 672-5399

Michele M. Simkin
Attorney for Applicants
Registration No. 34,717

Liliana Di Nola-Baron, Ph.D.
Agent for Applicants
Registration No. 56,073